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(54) Title: MODULATORS OF MOLECULES WITH PHOSPHOTYROSINE RECOGNITION UNITS

(57) Abstract

The present invention relates to novel organic compounds, to methods for their preparation, to compositions containing them, to their use for treatment of human and animal disorders, to their use for purification of proteins or glycoproteins, and to their use in diagnosis. The invention relates to modulation of the activity of molecules with phospho-tyrosine recognition units, including protein tyrosine phosphatases (PTPases) and proteins with Src-homology-2 domains, in *in vitro* systems, micro-organisms, eukaryotic cells, whole animals and human beings. The novel organic compounds are compounds of the general formula (I) $(L)_n-Ar_1-R_1-A$, wherein $(L)_n$, n, Ar₁, R₁ and A are defined as defined in the application.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 97/00166

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 231/00, C07D 257/00, C07D 271/00, C07D 285/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS, WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TETRAHEDRON, Volume 52, No 30, 1996, Bin Ye et al, "Synthesis of a Difluorophosphonomethyl-Containing Phosphatase Inhibitor Designed from the X-ray Structure of a PTP1B-Bound Ligand" page 9963 - page 9970	1-6, 8, 13-15, 18-22
A	---	7, 9-12, 16, 23-32
X	TETRAHEDRON LETTERS, Volume 33, No 29, 1992, Mark S. Smyth et al, "A General Method for the Preparation of Benzylic α, α -Difluorophosphonic Acids; Non-Hydrolyzable Mimetics of Phosphotyrosine" page 4137 - page 4140	1-6, 8, 13-15, 18-22
A	---	7, 9-12, 16, 23-32

Further documents are listed in the continuation of Box C.

See patent family annex.

• Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier document but published on or after the international filing date	"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
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Date of the actual completion of the international search

3 November 1997

Date of mailing of the international search report

04-11-1997

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 97/00166

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9507694 A1 (SANKYO COMPANY, LIMITED ET AL), 23 March 1995 (23.03.95), see particularly page 7	1-7,9-15, 18-22
A	--	8,16,23-32
X	WO 9640113 A2 (SUGEN, INC.), 19 December 1996 (19.12.96)	1-7,13-15, 18-22
A	--	8-12,23-32
X	WO 9112003 A1 (THE UP-JOHN COMPANY), 22 August 1991 (22.08.91)	1-7,13-15, 18-22
A	--	8-12,16, 23-32
X	EP 0764632 A2 (ELI LILLY AND COMPANY), 26 March 1997 (26.03.97), see particularly example 9	1-7,13-15, 18-22
A	--	8-12,16, 23-32
X	EP 0500337 A1 (UNIVERSITY OF COLORADO FOUNDATION, INC.), 26 August 1992 (26.08.92)	1-7,13-15, 18-22
A	--	8-12,16, 23-32
X	EP 0193256 A1 (TAKEDA CHEMICAL INDUSTRIES, LTD.), 3 Sept 1986 (03.09.86)	1-7,13-15, 18-22
A	--	8-12,16, 23-32

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 97/00166

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0339549 A2 (F. HOFFMANN-LA ROCHE AG), 2 November 1989 (02.11.89)	1-7
A	--	8-16, 18-32
X	STN International, File CAPLUS, Accession no. 1996:543848, Yanagisawa, Hiroaki et al: "Preparation of (azolylphenoxy)alkyl aryl or heterocycll sulfone derivatives having aldose reductase-inhibitory activity as hypolipidemics, hypoglycemics, and antiobesity agents", Jpn. Kokai Tokkyo Koho, 30 pp., Chemical Abstracts no. 125:195654	1-7, 13-15, 18-22
A	-- -----	8-12, 16, 23-32

INTERNATIONAL SEARCH REPORT

International application No.

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 17
because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1.(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
2. Claims Nos.: 1-7, 13-22
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

See extra sheet (*)
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See extra sheet (**)

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-32 and the first effect.

Remark on Protest

The additional search fees were accompanied by the applicant's protest.



No protest accompanied the payment of additional search fees.

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Box I

*Claims 1-7 and 13-22 have been searched incompletely. These claims are so broadly formulated that they include thousands of known compounds. These compounds differ structurally essentially from each other and the only uniting feature is the general definition of the effect (or rather the effects). The effects in claim 15 differ essentially from each other. Thus, the search has been limited to the combination of the too general definition of the compounds and the first mentioned effect in claim 15.

Box II

**As the uniting feature is considered to be the effect the following inventions comprising the corresponding compound, method of preparing, pharmaceutical composition, method of modulating, use for preparing medicament, method for purification and use in diagnosis can be seen:

- 1) diabetes, impaired glucose tolerance, insulin resistance, claims 1-32
- 2) obesity, claims 1-32
- 3) immune dysfunction...., claims 1-32
- 4) allergic diseases, claims 1-32
- 5) osteoporosis, claims 1-32
- 6) proliferative disorder...., claims 1-32
- 7)synthesis or effect of growth hormone, claims 1-32
- 8)synthesis of hormone or cytokines..., claims 1-32
- 9) diseases of the brain..., claims 1-32
- 10) infectious diseases, claims 1-32

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/10/97

International application No.

PCT/DK 97/00166

Patent document cited in search report	Publication date	Patent family member(s)		Publication date	
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Information on patent family members
01/10/97
International application No.
PCT/DK 97/00166

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